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Analysis of Clinical and Electrophysiological Findings in Jakob-Creutzfeldt Disease

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SUMMARY. Serial EEG and EMG investigations were performed in the course of a histologically verified case of Jakob-Creutzfeldt disease. Some electrophysiologic data, including visual-evoked responses were analyzed using a computer. Correlations between clinical and EEG findings suggest that the generator of the periodic discharges may be localized in some circumscribed area of the upper brain stem, probably the thalamus. The inhibitory effect of various narcotics suggests that the pacemaker of the triphasic discharges has relations to the nonspecific activating system.

KEY WORDS: Jakob-Creutzfeldt disease - EEG - Subcortical generator - Visual-evoked responses - EMG.

ZUSAMMENFASSUNG. EEG- und Elektromyogramm-Ableitungen eines Falles histologisch verifizierter Creutzfeldt-Jakob' scher Erkrankung werden im Verlauf beschrieben. Die Befunde werden durch visuell evozierte Reaktionen und durch Computer-Analysen ergänzt. Korrelationen der neurologischen- und EEG-Befunde machen es wahrscheinlich, daß der Generator der periodischen Entladungen im oberen Hirnstamm, vermutlich im Thalamus, lokalisiert ist. Hemmungswirkungen verschiedener Narkotica sprechen dafür, daß der Schrittmacher der triphasischen Entladungen Beziehungen zum unspezifischen aufsteigenden Aktivierungssystem hat.

SCHLÜSSELWÖRTER: Creutzfeldt-Jakob-Erkrankung - EEG - Subkortikaler Generator - Visuell-evozierte Potentiale - EMG.

Jakob-Creutzfeldt disease (JCD) is an infrequent neurologic disorder of the presenium, characterized by dementia, extrapyramidal signs, and unusual EEG patterns associated with myoclonic jerks. Recent evidence suggests it may be caused by some form of transmissible slow viruses (Gibbs & Gajdusek, 1969). The disorder is incurable, its average duration varies from 12 months to 2 years. Recognition of the EEG signs may be useful for an early diagnosis of the disease. The characteristics of the periodic bi- or triphasic discharges are well known (Jones & Nevin, 1954; Nagy, 1967), but the origin and mechanism of the EEG abnormalities are not well understood. Electrophysiologic data in correlation with clinical findings were analyzed in order to clarify this problem.

CASE REPORT

A 69-year-old woman was admitted to the psychiatric department because of severe deficits in mental functions. A month earlier she had complained about dizziness, and 2 weeks before she could neither walk nor eat alone. There was no abnormal finding in her internal status. Neurologic examination revealed normal ocular fundi, impassive facial expression, flexor-extensor type rigidity of the extremities, and mild weekness and hyperreflexia in her limbs, but the plantar reflexes were normal.Oral tendencies (sucking and bulldog reflexes) could be elicited. Psychiatric examination revealed torpor and lack of response to verbal stimuli. She had to be fed artificially because of dysphagia. At the time of the first EEG examination, no myoclonus was seen in the extremities; 2 weeks later some twinchings of the fingers and forearms appeared. Later the jerks became rhythmic and were pronounced in the left arm and face, sometimes with conjugated deviation of the eyes and sudden grimacing. Two weeks before death she was in decorticated posture, the plantar reflexes became extended. The jerks spread over the trunk and limbs. The patient died after 64 days in the hospital. Taking into account the catamnestic data, we estimate that the duration of the entire process lasted approximately 5 months.

The protein content of the cerebrospinal fluid was 23 mg% with beta and gamma globulin values at the upper limit of the normal. Neither cytopathogenic agents nor viruses were found. The cisternal pneumoencephalogram showed symmetrically dilated ventricles with abundant air filling of the frontal sulci. The blood gases in the internal jugular vein and femoral artery were determined several times radiometrically, and indicated decreased O_2 uptake and CO_2 production of the brain. Wassermann reaction in the blood was negative and the serum calcium, potassium, protein, blood urea, and sugar all were within the normal limits.

METHOD

Eight EEG and eight EMG investigations were made simultaneously. Silver-chloride electrodes were used, attached to the scalp with collodion, according to the 10-20 system. The EEG was recorded with a 16-channel "Orion" and a 12-channel "Hellige" polygraph. The EMG was recorded with a "Disa" electromyograph. The EEG and photic-evoked potentials were stored on magnetic tape (the 2-channel analog-digital transformer was constructed by Dr. L. Kellényi). Shape and phase relations of the triphasic complexes, as well as the visual-evoked responses, were computed on a NTA-analyzer. The brain and the spinal cord were examined by light microscopy.

RESULTS

At the time of the first EEG record the patient was unresponsive to verbal stimuli, but defensive reactions to painful stimuli were observed.

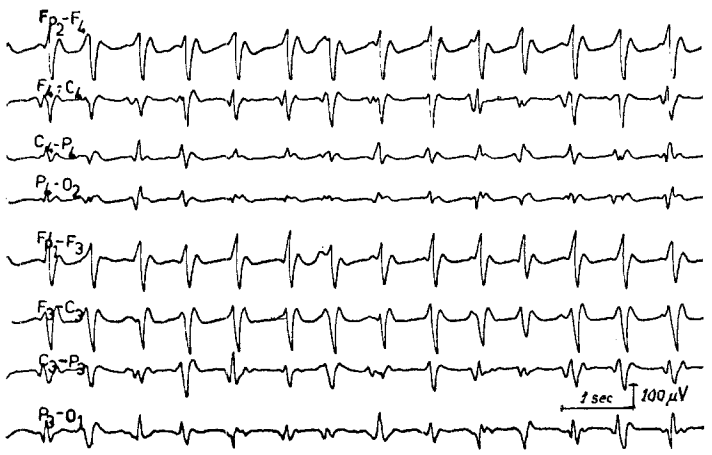

Fig. 1. Synchronous triphasic complexes in routine EEG tracing of both hemispheres

Bi- or triphasic sharp-wave complexes bursted synchonously in all leads with maximal amplitude in the frontal areas (Fig. 1). There was no constant periodicity of the complexes. The interparoxysmal intervals varied between 0.6 and 1.1 s. The irregular alpha activity gradually disappeared as the disease progressed, in the last record the background activity was nearly isoelectric between the complexes. The second (sharp) components of the triphasic complexes were generally surface positive in the longitudinal leads. In the transversal leads their phase was reversed between the left central and temporal regions. At the terminal stage of the disease the rhythm of the complexes became faster and more regular, the potentials were morphologically simplified. In the routine leads the complexes seemed to be perfectly synchronized. Phase and form analysis proved that the triphasic complexes appeared 22-26 ms sooner in the frontal than in the occipital region. Similarly, the complexes recorded centrally preceded those from the lateral areas by 25-30 ms. In the right temporocentral region the complexes were generated 29 ms earlier than in the corresponding left region (Fig. 2).

The amplitudes and waveforms of visual-evoked potentials over the right and left hemispheres were similar. The mean amplitude of 40 consecutive samples was 40 μV, which is within the normal range. The first surface positive component recorded on the right occipital region preceded the corresponding left side component (Fig. 3a). The first, surface positive component of the triphasic complexes on the right side, recorded by the same electrodes, similarly preceded the corresponding left side potentials (Fig. 3b).

The continuous burst of activity, lasting 2-3 s and accompanied by generalized myoclonic jerks could be supressed by painful, auditory stimuli and flashes. During the supression, irregular theta and alpha activity could be seen. There were no rhythmic responses to photostimulation at any frequency. The supression of complexes proved to be nonspecific, i.e., it did not depend on the modality of the stimuli. The cessation of the stimuli also caused supression of the complexes.

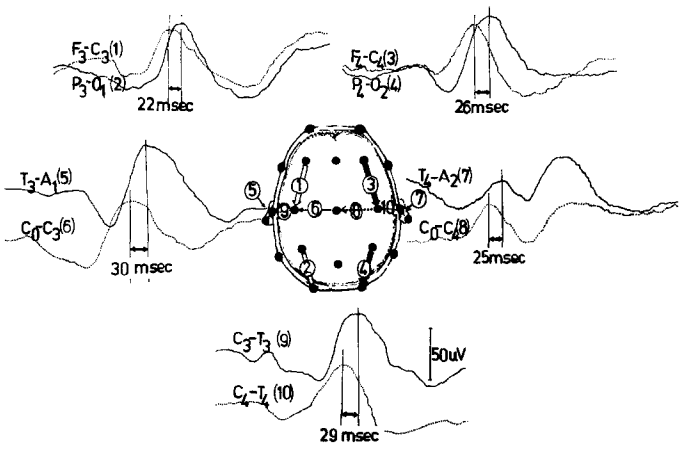

Fig. 2. Time relations of triphasic complexes recorded on various regions of scalp. Peak time intervals are indicated by arrows ⟷

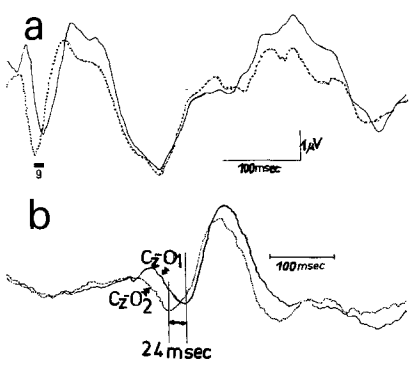

Fig. 3 (a) Average of 40 visual-evoked responses. The first - surface positive - component appeared 9 ms sooner on the right (C_z-O_2, dotted) than on the left occipital region (C_z-O_1, continuous). (b) Similarly, the first component of triphasic complex develops 24 ms sooner on the right (dotted) than on the left (continuous) hemisphere

The periodic fluctuation of the amplitudes was stochastic (Fig. 4). The arithmetic sum of the voltage of synchronous potentials (recorded in 16 channels) fluctuated in conjunction with the amplitude of single complexes recorded over the frontal region. Minimal and maximal values of two curves coincided. The most striking feature of the EEG abnormalities was the finding that the duration of interparoxysmal intervals varied proportionally to the second components of the triphasic potentials.

At the time of the first EEG record, sporadic unit discharges of deltoid muscles were recorded, which seemed to be independent of the EEG patterns. The rhythmic myoclonic jerks mostly coincided with the onset of the sharp components of the complexes (Fig. 5b). Sometimes the EMG po-

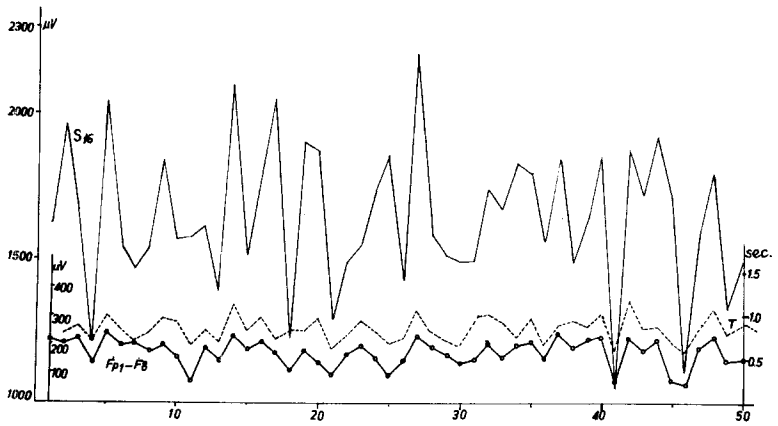

Fig. 4. Fluctuation in voltage and frequency of 50 consecutive complexes. Full line represents arithmetic sum of amplitude of 16 potentials which appeared synchronously in all channels. Broken line (T) indicates interparoxysmal periods in seconds (ordinate on right side). Bottom line shows voltage of complexes recorded from F_{p_2}-F_8

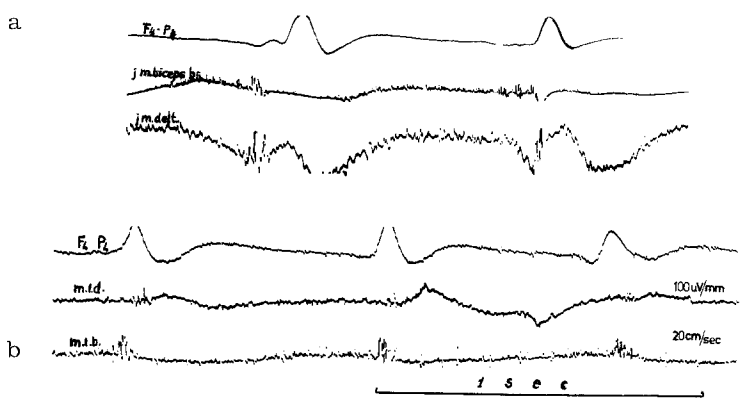

Fig. 5. First channel: EEG recorded from F_4-P_4. Second channel: EMG of right male biceps and femoralis. Third channel: right deltoid and tibialis. Upper curves (a): EEG potentials were preceded by discharges of myoclonic jerks. Lower curves (b): Myoclonic jerks coincided with sharp component of triphasic complexes

tentials preceded the EEG complexes, occasionally by 20 ms (Fig. 5a). The intensity of myocloni was inconstant. It was increased by arousal stimuli and decreased during resting.

Orally administered antiepileptics (diphenylhydantoin, Diazepam) did not alter the characteristics of the complexes. During drug-induced sleep a considerable change could be observed depending on the chemical structure and dose of the compounds. Diazepam had marked effect on the amplitude of complexes (Fig. 6a). Initially, the amplitude of the second components decreased and the first (surface negative) component disappeared. The frequency of the complexes decreased in proportion to their voltage but periodicity remained recognizable. About 400 s after the injection, the third (surface negative) potential became dominant. The duration of the triphasic complexes increased proportionally to the interparoxysmal intervals. There was no frequent burst of activity which otherwise is characteristic of Diazepam-induced sleep. The effect of Sombrevin (3 metoxy-4NN-diethylmetoxy-phenilacetic-propilester) markedly differed from the effect of Diazepam. The second sharp components were preserved with slightly decreased amplitude, but the interparoxysmal intervals were five to six times longer than those during resting. At the maximum of the Sombrevin effect, the interparoxysmal activity disappeared (Fig. 6b). No characteristic theta activity was seen as an effect of the drug. The modifying effect of the barbiturates was the same as found by previous investigators. During superficial drug-induced sleep, arousal reactions could be elicited. Over the occipital regions the inhibited complexes reappeared, and fragmented alpha activity could be evoked by painful stimuli.

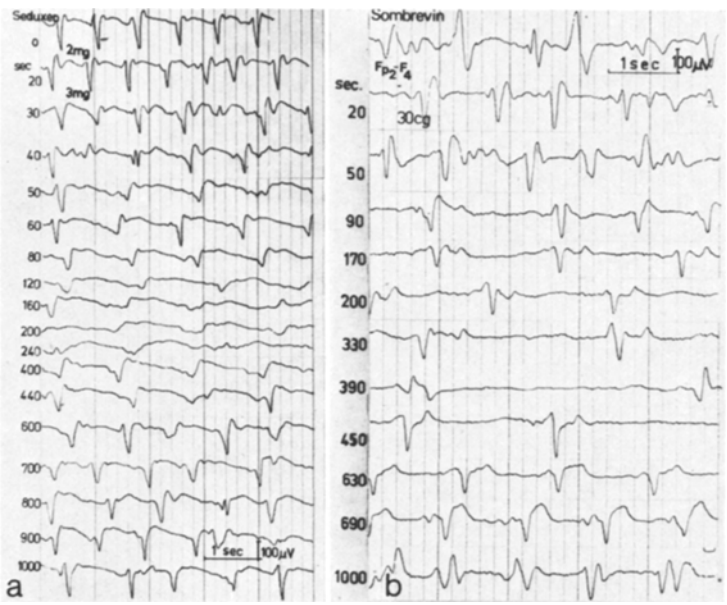

Fig. 6. Effect of Seduxen (Diazepam) (a) and Sombrevin (b) on triphasic complexes

DISCUSSION

There are no degenerative or inflammatory diseases that exhibit EEG patterns identical with those seen in Jakob-Creutzfeldt disease. The most characteristic feature of the electrical patterns in JCD are their constant periodicity and wave morphology. The polyspikes in progressive myoclonic epilepsy mostly occur sporadically and the generalized abnormalities show no constant periodicity (Koskiniemi, 1974). In subacute progressive panencephalitis the slow wave complexes and the interparoxysmal periods are longer and irregular when compared with JCD. The EEG abnormalities in some cases of Alzheimer's disease are not identical with, but only "to a certain extent homologous" to EEG changes in JCD (Jacob, 1970).

The opinions on the origin of the pathologic EEG patterns are quite diverse in the literature. Jacob et al. (1958) found a correlation between EEG complexes and EKG. In our case no consistent coincidence of the two phenomena could be found. The primarily cortical origin of the periodic discharges was stressed by Jones & Nevin (1954) on the basis of the similarity between the Matrazol effect on the cortex and the triphasic complexes observed in JCD. Gloor et al. (1968) studied the EEG changes in diffuse encephalopathies. They concluded that involvement of subcortical and cortical gray matter is an important factor in the genesis of the paroxysmal bilateral synchronism. This feature of electrical disturbance appeared, regardless of the presence or absence of white matter lesion. JCD may be classified with this group, according to the histopathologic findings. Notably, lesions of the white matter are generally less severe in comparison to those of the cortex and subcortical gray matter (Nevin et al., 1960). Mayerdorf & Förster (1973) suggested that selective alteration of the medial thalamic nuclei are related to the pathologic EEG of the disease. Rayport (1963) studied the electrical activity of JCD with scalp, pial, and intracerebral leads. He observed high voltage positive-negative spikes and triphasic waves at the pial and scalp recordings. These potentials were similar (both in amplitude and form) to those recorded in the globus pallidus. This was interpreted as indicative of two separate (cortical-subcortical) generators of the periodic bursts. Nelson (1968) also recorded from several subcortical centers. His findings proved that the EEG patterns did not arise from the cortex, but were volumeconducted potentials generated by a single source within the thalamic nuclei. On the basis of the analysis of visual-evoked potentials, Lee & Blair (1973) suspected the periodic discharges to originate from "some subcortical area functioning as a pacemaker."

We did not see the decline in frequency of the periodic discharges that had been reported by many authors at the terminal stage of the disease. The probable reason may be that the patient died of intercurrent complications before the degenerative process ended.

The dominant frontotemporal projection and the phase relations of the discharges show that they originate from the upper brain stem. This is in accordance with Nelson's conclusion cited above. One linear vector of electrical impulses, arising from the brain stem, spreading up- and downward could be constructed. The presence of an arousal reaction (reappearing of the complexes with desynchronization of the background activity) produced by external stimuli during induced sleep suggests that the

"trigger zone" may have functional connections with the ascending reticural system. The inhibitory effect of narcotics on the frequency and shape of the complexes was observed by many authors (Richter, 1968; Lee & Blair, 1973; Mayerdorf & Förster, 1973; Elliot et al., 1975; Ott & Despland, 1975). Our findings are in accordance with these results. Both the amplitude and frequency of the complexes were reduced proportionally under the effect of narcotics. It was postulated that the pacemaker of the EEG complexes might be a closed neuronal circuit, acting in a cybernetical sense, as time-energy integrated system. All the stimuli (internal, sensory, drugs) that modify the frequency of impulses could also modify their energy (amplitude).

The myoclonic jerks and their relation to the EEG complexes in JCD resembled those reported by Cobb (1966) in a case of subacute sclerosing encephalitis.

In our case the myoclonic jerks sometimes preceded the EEG complexes by 20-50 ms. This finding makes it probable that in some instances the pacemaker of the periodic complexes lay nearer to the muscles rather than to the cortex. This, of course, would not mean distance in space, but only varying conduction velocity from the generator elements toward muscle and cortex.

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